PRIMARY TUMORS OF THE ADRENAL GLAND IN CHILDREN.

REPORT OF A CASE OF SIMULTANEOUS SARCOMA OF THE ADRENAL GLAND AND OF THE CRANIUM, WITH EXOPHTHALMOS.

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Tumors of the adrenal gland in childhood are not only very rare, but the histology of those that have been reported has not been, as a rule, thoroughly studied. Furthermore, they present in their clinical course differences from the adrenal growths of adults, and tend to fall into rather definite types, with clinical characteristics which may permit of an accurate diagnosis during life. For these reasons we report the following case, remarkable from both the clinical and the pathological point of view.

G. H. C., a male infant, aged sixteen months, entered the Massachusetts Charitable Eye and Ear Infirmary, September 10, 1906, in the service of Dr. Alexander Quackenboss, to whom we express our thanks for turning over the case to us for publication. The family history was excellent, the past history good up to the early part of August, 1906, when a purple discoloration of the upper and lower lids of the right eye suddenly appeared. On August 26 the child was examined by Dr. Myles Standish, who found exophthalmos of the right eye, with diffuse hemorrhagic infiltration of the upper and lower lids; the pupil unresponsive to direct light, but contracting when light was thrown into the other eye. A soft mass over the right temporal region, said to have been present two days, was noted; it measured 1½ x 2 x 3 inches. The fundus was normal.

On entrance to the hospital the ecchymosis of the lids was very marked, with considerable protrusion of the eyeball directly forward. The latter was immobile and vision was apparently *nil;* there was no injection of the conjunctiva. A large flat swelling extended outward from the orbit to the right temporal region, reaching back as far as the ear, and involving the whole temporal region. It was smooth, rather tense, and semifluctuating, the overlying skin not adherent, but showing dilated veins. The corresponding pre-auricular lymph nodes and those at the angle of the jaw were considerably enlarged. The left eye was normal; the nose and throat, heart, lungs, and abdomen were negative on physical examination; the spleen and liver were not enlarged.

Blood examination: leukocytes, 12,000. Smears examined September 17 by Dr. W. H. Smith showed no achromia, and a differential count as follows: polynuclear neutrophiles, 55 per cent.; mononuclears, 44.5 per cent.; eosinophiles, 0.5 per cent.

During the three weeks stay in the hospital, the exophthalmos increased slightly, the temporal growth and the metastases in the lymph nodes grew a good deal larger, and a slight ecchymosis appeared on the lower lid of the other eye. The lids on the right side had become almost black. There was slight injection of the palpebral and the ocular conjunctiva. On September 23 a small piece of the enlarged glands in front of the ear was removed for examination. It was of a bluish color (owing to hemorrhage), and was reported by the pathologist, Dr. F. H. Verhoeff, to be a small round-cell sarcoma.

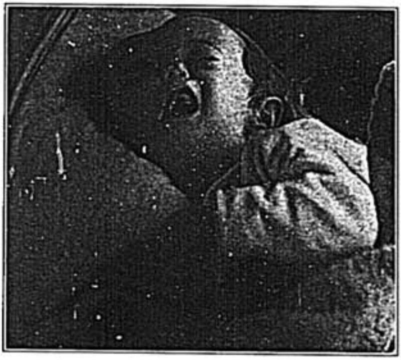
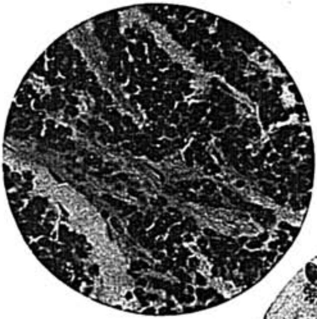


FIG. 1.—Appearance of the child shortly before death.

The patient was given a careful general examination by Dr. W. H. Smith, and later by one of us (Tileston); no abdominal tumor could be made out, although one was looked for. The patient was sent home to West Springfield, New Hampshire, October 2, 1906, and was cared for there by Dr. D. P. Goodhue, to whom we owe thanks for further notes and for obtaining permission for the autopsy. The infant soon fell into a deplorable state, with almost constant pain in the region of the right eye, which almost entirely left its socket, being pushed outward, downward, and inward, so that it nearly touched the nose. The growth about the temple took on huge proportions (Fig. 1), and the cachexia increased. The patient died January 13, 1907.

Autopsy at West Springfield, N. H., thirty-two hours postmortem (Harvard Medical School Series, 3297): The body is that of an



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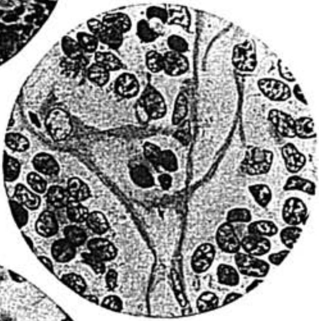

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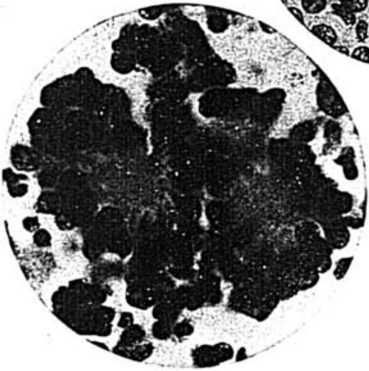

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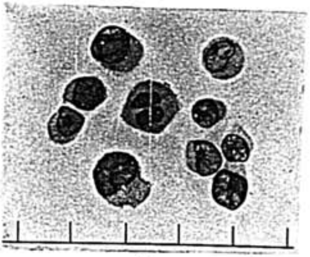
FIG. 2.—Photomicrograph of a section of the tumor, to show the general arrangement in the denser portions. (330 diameters.)

FIG. 3.—Drawing reduced from fifteen hundred diameters, to show the reticular supporting tissue.

FIG. 4.—Photomicrograph of two rosettes. (660 diameters.)



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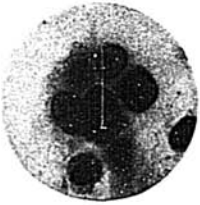

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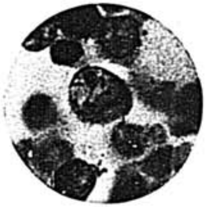

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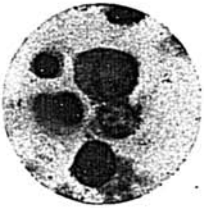

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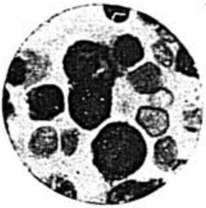

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FIG. 5.—Drawing of single tumor cells, showing the variation in size and also a cell in mitosis. Each division of the scale equals ten microns.

FIGS. 6, 7, 8.—Photomicrographs of tumor cells, showing details under high power for comparison with Figs. 5 and 9. (1140 diameters.)

FIG. 9.—Photomicrograph of myelocytes from the erythroblastic liver of an infant. From a case of severe anemia with splenomegaly.

emaciated, poorly developed male infant, 79 cm. long. There is no rosary. The head is greatly deformed and turned to the right. There is marked œdema of lower limbs, penis, and scrotum. The legs are covered with numerous, small, red areas which do not disappear upon pressure. There is a large decubitus on the right hip, exposing the great trochanter, which is denuded of periosteum; and a small decubitus upon the back at the costal angle below the left scapula. There are prominent lymph nodes on the right side of the neck, at the angle of the jaw, and along the sternomastoid muscle; the lymph nodes elsewhere are not palpable.

The deformity of the head is due chiefly to a huge tumor mass on the right side, covering the forehead and frontal bone, and producing great prominence of the zygoma, which is freely movable and pushed forward and downward. The right eye is pushed forward and is directed inward; the sclera is loose; the cornea is clouded. The alveolar process of the superior maxilla is asymmetrical, presenting a greater convexity on the right side. The buccal surface of the palate is convex. The general contour of the right side of the face is convex, due to a diffuse tumor, involving the parotid region as well as the parts described above. There is marked œdema of the scalp and face on the right side. Over the right inferior occipitoparietal angle is a large, rounded, boggy eminence about 11 cm. in diameter. The whole right side of the scalp and face is dark reddish blue in color. The consistency of the tumor over the forehead is soft and elastic, not fluctuating. The following measurements were taken: circumference of head, at level of left frontal eminence 53 cm.; from anterior fontanelle to symphysis of inferior maxilla, right side, 27.5 cm.; left side, 22 cm.; from external auditory meatus to midline, determined by the teeth, right side, 13 cm.; left side, 9.5 cm.

There is no subcutaneous fat and no fat in the omentum, mesentery, and about the kidneys. The omentum is thickly sprinkled with small black dots and irregular black areas, without thickening (old hemorrhages). The peritoneal surfaces are everywhere smooth, moist, and glistening. The colon is inflated in some places; in others contracted and injected about hardened masses of feces. The mesenteric glands are not remarkable. The appendix is normal. The diaphragm reaches to the fourth rib, left; third interspace, right. In the right side of the abdomen, behind the ascending colon, and compressing the kidney and pushing up upon the liver, is an irregular, soft, elastic tumor mass. The shape is roughly that of a flattened ovoid with a broad lateral process crossing the spine. The posterior portion of the right lobe of the liver is flattened horizontally, and is adherent to the tumor. The right kidney is flattened to one-half of its normal thickness, as far down as the junction of the lower and middle thirds. The lower border of the tumor is at the level of the middle of the fifth lumbar vertebra. The inferior vena cava runs through the anterior portion of the tumor, 0.5 cm. below the anterior surface, and lies 4 cm. to the right of the spine and 1 cm. anterior to its normal position; it is flattened and completely surrounded by the tumor mass, as far down as the point where it is crossed by the common iliac artery. In the upper portion of the vena cava just before it leaves the tumor, there is a small flattened, mural thrombus of friable, grayish red clot. The lower portion of the tumor crosses the spine, and lies upon the aorta and pelvis of the left kidney, and compresses both of these structures. The tumor is not adherent to either kidney, and all surfaces are invested with a thin, fibrous capsule. The dimensions of the tumor, measured in situ, are: Vertical diameter, 12 cm.; transverse diameter along the lower portion, 8 cm.; anteroposterior diameter, 8 cm. On section, the tumor is made up of spherical masses of pale, translucent, grayish, soft, elastic tissue, with large areas of hemorrhage and necrosis. In the upper portion the adrenal gland is included. The superior border of the adrenal is intact; the medulla of the bulk of the gland is continuous with the tumor tissue, while the cortex of the lower part diverges to include a dark red, spherical mass, 1 cm. in diameter, and is then gradually lost in the tumor tissue, running for some distance as faint yellow lines. The compressed portion of the liver is not invaded by the tumor. There are several smaller spherical and flattened spherical masses, 1 to 2 cm. in diameter, attached to the various surfaces of the larger tumor. These on section prove to be continuous with the main tumor body, while the external surfaces are covered with a thin, smooth, fibrous membrane.

The pleural cavities are normal; no free liquid; no adhesions. The thymus gland is small; estimated weight, 1.5 grams. The pericardial cavity is normal and the heart is normal in size. The myocardium is of good color and consistency. The valves and endocardium are normal. The foramen ovale is closed. The lungs are uniformly soft, pale, and downy, with the exception of narrow lines of postmortem settling on posterior borders. Bronchial nodes not remarkable.

The spleen is large; length, 6 cm.; breadth, 4 cm. The proportions are normal, and the capsule is smooth. The color and consistency are normal. The liver is 13 cm. in breadth; antero-posterior diameter of right lobe is 9 cm. The posterior portion of the right lobe is compressed by the abdominal tumor described. The color and consistency are normal. The gall-bladder and ducts are normal. The gastro-intestinal tract is normal except for small areas of injection in the colon, in portions contracted about hardened feces.

The pelves of both kidneys are much dilated and contain numerous soft, brownish masses of granular material. Both kidneys smooth non-adherent capsules. The color is normal. The glomeruli are visible. The upper ends of both ureters are slightly dilated. The right kidney has a concave anterior surface, corresponding to the upper two-thirds which was in contact with the tumor mass in the abdomen. This portion of the kidney is about one-half the thickness of the lower third, and slightly broader.

The pancreas, bladder, testicles, and thoracic duct are normal.

The organs of the neck are normal. There is a large mass of soft pink and deep red glands at the angle of the jaw. Those along the sternomastoid are firm, large, and gray.

The femur, vertebræ, sternum, and ribs are normal. All contain red marrow.

The hair of the head is short and sparse; dark-brown. The scalp and skin are much thinned on the right side of the face. The scalp is markedly œdematous, particularly over the right lower occipitoparietal angle. Beneath the aponeurosis of the whole frontal regions is a soft elastic tumor mass, deepest just below the frontal eminence, where it is 5 cm. deep. Superiorly and laterally the mass gradually diminishes in depth. Inferiorly it is continuous with the tumor tissue on the side of the face and behind the zygoma. The right parietal bone slightly overrides the left, and the parietal suture is studded with small, soft, reddish elevations. The anterior fontanelle is 1 cm. in diameter. On removal of the calvarium, a large, extradural tumor mass is found to fill the whole anterior fossa of the skull. This tumor mass is 6 to 7 cm. deep, and is continuous with the tumor mass on the external surface, through an opening in the frontal bone directly over the orbit. The opening, as near as can be determined, is 2 to 3 cm. in diameter. The adjacent bone is covered on all sides and both surfaces with necrotic and hemorrhagic tumor tissue, and sends innumerable delicate bony spicules into the substance of the tumor. The whole of the tumor within the skull is dark red, in places very soft and necrotic. The orbital plate on the right side is elevated and eroded. All of the accessory sinuses, the antrum of Highmore, and the nasal cavity are filled with dark red, soft, tumor tissue. The internal surface of the dura over the vertex is thickly studded with soft, translucent, grayish nodules, 1 to 3 mm. in diameter. The dural sinuses are normal. The tumor superiorly extends backward between the dura and bone within the skull as far as the lambdoidal suture. On the left side it extends 2 to 3 cm. beyond the median line. The left orbital plate is recessed, and the posterior part of the orbit contains tumor tissue. The pituitary body cannot be found. There is marked deformity of the floor of the skull; the basilar process of the occipital bone is directed inward to the left. The sella turcica is flattened. The general shape of the skull is that of a distorted ovoid, inclining toward the right.

There is marked asymmetry of the brain. The right half of the frontal region slopes obliquely toward the left; the frontal lobe is flattened, as far back as 2 cm. from the tip of the temporal lobe. Both tips of the frontal lobes are flattened and slope obliquely upward

The olfactory processes are small, flattened, and lie parallel with the median fissure, which is directed toward the left. The pia is normal. The convolutions are slightly flattened over the regions already indicated. Elsewhere there is no flattening. The consistency of the brain is moist and soft (postmortem?). Nothing abnormal is found on section of the hemispheres, pons, basal ganglia, medulla, and cerebellum. The vessels at the base are normal.

Anatomical Diagnosis. Sarcoma of the cranial cavity; sarcoma of the right adrenal; emaciation; deformity of the skull and brain, due to a growth under pressure; œdema of the lower extremities due to pressure on the abdominal vessels; mural thrombus of the inferior vena cava.

Microscopic Examination. The following stains were used after Zenker fixation: methylene blue and eosin; Mallory's connective tissue stain; and Mallory's phosphotungstic acid hemotoxylin stain.

Portions of the mesentery containing the dark spots, when treated with potassium ferrocyanide and hydrochloric acid, give the reaction for iron-containing pigment.

The heart, liver, pancreas, adrenal, testicle, and mesenteric lymph nodes are negative.

Spleen. The corpuscles are of good size, symmetrical and abundant, but contain few active cells. The pulp is moderately injected. Both pulp and corpuscles contain numerous polymorphonuclear eosinophiles. A large lymphatic accompanying a branch of the splenic artery at the hilum is tightly packed with small round cells, which on one side are invading the surrounding connective tissue. These cells have round or oval nuclei 5 to 8 microns in diameter. The nuclei stain deeply with the basic stain, and have a coarse basic-staining reticulum, usually with a large chromatin mass at the centre and other smaller masses scattered throughout. The protoplasm cannot always be made out. In places it occurs as a narrow, pinkish, finely granular, eccentric band, without a membrane.

Kidney. The cells of the convoluted tubules are swollen and granular. There are numerous hyaline casts in the collecting and Henle tubules. There are many imperfectly developed glomeruli.

Thymus. The lobules are very small and contain much hyaline connective tissue. The epithelial rests are very small and completely converted into hyaline-like material. There are very few cells resembling lymphoid cells, and the bulk of the cells are spindle-shaped connective tissue cells.

Cerebrum. Temporal Lobe. There is apparently an increase of cells resembling the satellite cells throughout the cortex. The ganglion cells are small; they are usually surrounded by a clear space. The protoplasm is broken up into groups of granular material, and the nuclei are surrounded by clear spaces, so that the cell outlines are indicated by rather narrow fringes of granular protoplasm (postmortem change?). No Nissl granulations are visible. A few ganglion cells contain minute rings of eosin-staining material. The nuclei are deeply stained with the blue; a few are large and vesicular.

Tumor. The arrangement is that of closely packed, small, round cells, supported by a delicate connective tissue reticulum. In places the cell groups are divided by the reticulum into round or irregular and elongated masses (Figs. 2 and 3). In many places the cells are arranged two to four deep in rosette form about masses of eosin-staining, finely granular material; the groups vary from 20 to 70 microns in diameter. This rosette arrangement occurs in all the sections taken from different parts of the growth, in the abdomen, glands, upon the dura, and in the head (Fig. 4). Where the tumor is invading the frontal muscle and adrenal this arrangement ment does not occur. The abdominal mass has completely surrounded the adrenal, and has destroyed the major portion of it, apparently by pressure, as the capsule and cortex are invaded in only a few places. Dilated lymphatics of the adrenal capsule are filled with tumor cells. In some places there is a definite invasion of the cortex with disappearance of the capsule. A lymph node from the angle of the jaw is completely filled with tumor masses, large hemorrhagic foci, and necrotic cells. Here the arrangement is chiefly in rosettes. The reticular structure of the lymph node is present only in places.

Everywhere throughout sections of the tumor from all locations, there is much necrosis of the tumor cells, resulting in hyaline eosin-staining bodies containing one or several irregular-shaped basic-staining granules. The tumor cells are about the size of the largest myelocytes found in erythroblastic centres in bone marrow (Figs. 5, 6, 7, and 8). The nuclei are 5 to 8 microns in diameter. There is very little protoplasm, often none is demonstrable. Usually the protoplasm is eccentrically arranged. It stains purplish, is finely granular, and has no cell membrane, nor granular inclusions. Often the cells of the rosette groups are elongated; the protoplasm is drawn out radially on the central side of the nucleus. Occasionally the nucleus is egg-shaped, with the small end toward the centre of the group. The nuclei, as a rule, are round or oval, and vesicular in appearance. A few show peripherally arranged chromatin masses, but the general distribution of chromatin is a scattered one throughout the nucleus. There is usually a central basic-staining round mass, larger than the scattered chromatin material. The nuclear reticulum is coarsely meshed and very prominent. A few mitotic cells are found. There is evidence of direct nuclear division in the shapes assumed by large nuclei, and the frequent presence of two nuclei in one cell.

The phosphotungstic acid hematoxylin stain reveals no fibrils connected with the tumor cells.

The cells undergoing mitosis are a trifle larger than the other tumor cells; the one illustrated is 10 microns in diameter. The protoplasm is a purplish pink and finely granular. At the periphery of the protoplasm there are usually numerous, small, deeply stained basic granules (Fig. 5). In all portions of the tumor there are many cells with perfectly definite, abundant, coarsely granular protoplasm, with nuclei which are small, densely colored with the basic stain, and separated from the protoplasm by a narrow, sharply demarcated, unstained space. These are probably degenerated cells (Figs. 6, 7, and 8). The reticulum consists of a delicate fibrillar connective tissue, accompanied by large cells resembling those of embryonic connective tissue (Fig. 3)..

In all sections of the tumor which include adjacent normal tissues, the veins and lymphatics of the latter contain clumps and often rosettes of tumor cells. In the dura there are tumor cells in the veins, from which invasion of the tissues is apparently taking place.

The marrow from the femur shows normal active marrow, with many small groups of tumor cells, ranging in size from closely packed groups of six to ten cells, to masses 1 mm. in diameter, showing the characteristc groupings and type of cells occurring elsewhere in the tumor.

Summary and Classification of the Tumor. In this case the striking pathological feature is the finding of large identical tumors in the abdomen, involving only the adrenal, and in the cranium, involving only adjacent soft tissue and lymph glands. In spite of the frequent finding of tumor cells in the bloodvessels and lymphatics, metastases were found only in the bone marrow and the lymph nodes of the neck. The slight tendency to invasion is shown by the presence of a large portion of intact adrenal in the abdominal tumor mass, and in the flattening of the liver and kidney, without extension into either. The tumor is a small round-cell sarcoma. belonging to the type in which the cells are supported by a reticulum. The cells resemble the undifferentiated cells of the bone marrow.

In the classification of this tumor, it should unquestionably be placed in that group of tumors which includes all those derived from the blood-forming cells, both white and red. Ribbert has proposed the name lymphocytoma for this group, which includes all those tumors called malignant lymphoma (lymphosarcoma, malignant lymphadenoma, etc.), chloroma, myeloma, and possibly the leukemias. The essential features of this group are the reticular supporting tissue, and the type of tumor cell, which represents a more or less incompletely differentiated cell belonging to the blood forming series.

Two characteristic tumors of this group present cells in which the type is readily recognizable; the myeloma, in which the cells resemble very closely certain cells found normally in the bone marrow and probably identical with plasma cells, and the lymphoma, in which the cells resemble either differentiated lymphoid cells, or the cells of the germinal centres of lymph follicles.

The peculiar grouping of the tumor cells in rosette arrangement, shown in Fig. 4, deserves consideration. Unlike other tumors in which there is a rosette arrangement, certain gliomas, for instance, there is no attempt at lumen formation. In no instance could vessels or connective tissue, or remains of either, be found in the centres of these groups. The examination of many sections has proved the shape of these clumps of cells to be roughly spherical or ovoid, thus excluding the possibility of columnar growth about a supporting tissue, which in cross section might give such an appearance.

While these rosettes are found in all portions of the tumor, they are most common in those parts where there is least supporting tissue, and are found even in the metastatic masses of cells within bloodvessels. The possibility of an agglutinative phenomenon is perhaps worthy of mention, because of the suggestion that the cells, in the absence of a supporting tissue and because of the very soft consistency of these portions of the tumor, were suspended in a liquid or semiliquid medium. This is also suggested by the presence of a very fine granular deposit, which stains lightly with eosin, resembling that thrown down by Zenker's fixative from liquids containing albumin. The granular central substance of these clumps can also be explained by this hypothesis, while it is otherwise difficult to account for it, because in the absence of nuclear remains, it is not probable that it is derived through the degeneration of cells.

Another perhaps more plausible explanation is that the tumor cells, after multiplication, have failed to separate from one another, and by their cohesion produced the rosette arrangement. Until a number of tumors similar to this one have been accurately described it is best not to attempt to select a descriptive name.

For clinical purposes, tumors of the adrenal gland in children may be divided into four classes: (1) Those with metastases to the skull (Hutchison's type); (2) those of simultaneous sarcoma of the liver and adrenal; (3) those associated with precocious maturity; and (4) those not falling under any of the preceding headings.

It is in connection with the first of these types that the foregoing case is important. Hutchison has recently called attention to this new clinical syndrome, and has reported 10 cases, 6 hitherto unpublished, and 4 from the literature. In view of the rarity and great interest of this condition, it has seemed desirable to collect and analyze as many cases as possible. We have reviewed the literature carefully, and have succeeded in adding 4 new cases to the list, while we have left out one of those included by Hutchison (that of Ogden and Mathews), for reasons that will be given later. This brings the total number of cases reported up to the present time, including our own, to 14.

The following description applies to Hutchison's type of adrenal tumor (the others will be considered later). This syndrome has been found hitherto only in infants or young children, and shows the following characteristics: Spontaneously or after trauma there appears ecchymosis of one or more eyelids, soon followed by exophthalmos, which is usually one-sided. The eye becomes more and more protruded, and there appears a growth in the adjacent temporal region, with enlargement of the lymph nodes in front of the ear and at the angle of the jaw. A tumor in the region of the kidney is felt during life in the minority of cases (6 out of 14); most frequently, as in our case, it constitutes one of the surprises of the postmortem table. The orbital tumor grows with great rapidity, and death ensues early from cachexia and anemia. Optic neuritis may occur, but total blindness is the exception. Pain in the head is frequent, but vomiting, in spite of the extension inward toward the brain, is rare. The abdominal growth may be quite large, and is then accompanied by swelling of the superficial abdominal veins, but never by ascites. Fever is usually absent. The urine, in the few instances in which it has been examined, has been free from blood and albumin, except in Aisenstein's case, in which albuminuria was present. The blood shows a secondary anemia, which may become extreme; there was reduction of the red cells to 1,400,000 in one case. The white cells are not increased, but there is usually a relative decrease of the polynuclear neutrophiles; whether the increase in basophiles affects the lymphocytes or the cells probably originating in the bone marrow (pre-myelocytes and allied forms) does not appear from the details reported, polynuclears only being mentioned.

The early age of the patients deserves especial emphasis. Twelve of the 14 were not over three years of age; 4 were under one year; 2 between one and two years; 6 between two and three years; only 2 were over three years; the eldest being nearly nine years old. The male sex predominated, with 9 boys to 4 girls (the sex is not stated in one case).

Pathological Anatomy. The adrenal growth varies from the size of a walnut to that of a child's head. It is usually one-sided, the right and the left side being involved with almost equal frequency. On section the surface is smooth, gray-white or yellow, and mottled with hemorrhages. There is little tendency to invade the neighboring tissues and organs. Metastases to the calvarium were present in all cases, to the ribs in 4, to the spine and tibia in 1 each; in 1 case the bone marrow and periosteum of several of the long bones were involved. In this connection it is interesting to note that of the cases of primary adrenal growths in children in the literature, in which the cranium was not involved, not one showed metastases to other bones, with the exception of Caillé's[1] case, which is incompletely reported. In Cohn's case, besides the cranial growths, almost all the ribs showed metastases at the junction with the costal cartilages, presenting a picture like that of rickets, and as he points out, the great vascularity and rapid growth of these parts in infants may well be the reason for the preference shown to the skull and ribs in both diseases. In spite of the large size of the growths in the skull, the brain is not invaded. Of other organs, the liver, kidneys, and lymph nodes were most often the seat of metastases; the ovaries once.

Histology. These tumors are almost invariably sarcomas; in 3 cases only was another diagnosis made, that is, hypernephroma twice, and melanotic carcinoma. Five of the 14 showed practically the same structure, being classed either as small round-cell sarcoma (3 cases), or as lymphosarcoma (2 cases). Three are described as "round and oval-cell sarcoma," 1 as "medullary sarcoma," and 1 simply as "sarcoma." One case is reported without microscopic examination.

In view of the rarity of the condition, we shall give a brief description of the cases hitherto reported, in chronological order. The 6 original cases of Hutchison are designated by the numbers they bear in his table.

CASE I. Cohn. Female child, aged nine months. First symptoms, "boil" on the right temple and exophthalmos of the right eye; soft semifluctuant flat tumor in the right temporal region attached to the bone; five similar smaller tumors behind the left ear; deep in the right flank a tumor not connected with the liver; spleen and liver enlarged; no blood or albumin in the urine; tremendously rapid growth of the cranial and abdominal tumors; great enlargement of the occipital and deep cervical lymph nodes; no fever; death in five weeks. At autopsy a large tumor of the right adrenal, with secondary nodules in the right kidney, liver, ovaries, and most of the ribs at the junction with the costal cartilages. Virchow diagnosticated "medullary sarcoma," primary in the adrenal.

CASE II. Reimann. Female infant, aged three months at the onset; first symptom, subcutaneous nodules of a bluish color; these did not increase in size, but fresh ones continually appeared; no exophthalmos, but two small periosteal tumors on the parietal bones; death at the age of seven months. At autopsy primary tumors of both adrenals, very numerous metastases in the bones, subcutaneous tissues, muscles, dura mater, and liver; metastases in both parietal bones, in the marrow of the long bones, and also in the periosteum of these bones. Chiari made the diagnosis of melanotic carcinoma; microscopically the tumor consisted of round and

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[1] Archives of Pediatrics, 1895, xii, 594.

"epithelioid" cells arranged in islands separated by connective-tissue septa, and bearing large masses of granular pigment.

CASE III. Barnard (Case V of Hutchison). Boy aged two and one-half years; fall on the head six weeks previously; next day cheek and eyes swelled; on examination entire head enlarged, both eyes forced out of their sockets, soft tumor masses on the forehead; in the left hypochondrium an irregular tumor lying deeply, with the intestine in front of it. Red cells, 3,200,000; whites, 8400; polynuclears, 47 per cent. The correct diagnosis was made during life; at autopsy sarcoma of the left adrenal, infiltration of the calvarium with newgrowth, a small metastasis in the liver.

CASE IV. Aisenstein. Boy, aged two years. First symptoms, anemia, loss of weight, pain on walking or standing. Fever throughout the disease. Albuminuria, dulness in chest due to enlarged mediastinal glands. A month after admission hemorrhage into left eyelid. Hemorrhagic pleural effusion. Lateral displacement of lower dorsal vertebræ. Finally large tumor on frontal bone, large deep-seated mass in region of stomach, small scattered round tumors in abdomen. Marked anemia; death at the end of three and one-half months. Clinical diagnosis, tuberculosis. At autopsy large tumor of left adrenal, with numerous metastases to the skull and ribs, also to the abdominal, mediastinal, and cervical lymph nodes, and to the pancreas. Microscopically oval and polygonal cells with alveolar arrangement; the tumor is classified as an alveolar sarcoma or endothelioma, belonging to the hypernephroma group.

CASE V. Bruck. Female, aged one year and two months; first symptom pain in the abdomen with swelling, then discoloration and swelling of the right eyelid; no exophthalmos. Tumor of the liver reaching nearly to the anterior superior spine of the ileum. Exploratory operation; death the same day. At autopsy a tumor of the right lobe of the liver the size of a child's head, and of the right adrenal the size of an apple; smaller tumors on the upper wall of the orbit, and in the dura of the frontal bone. Tumors of liver and adrenal not continuous; pancreas involved by extension. Microscopic examination, small round-cell sarcoma.

CASE VI. MacCarty. Child (sex?), aged two and one-half years. Eight weeks before entrance to the hospital a small "boil" on the left side of the head. Soon after, right exophthalmos, enlarged glands behind the ear and in the left axilla; abdomen distended. A small tumor in the jaw appeared, following the extraction of a tooth. On examination a fluctuant tumor the size of a large apple in the left parietal region; a smaller tumor in the left axilla; right exophthalmos; liver three fingers' breadth below the ribs; spleen palpable. Blood: polynuclears, 70 per cent.; lymphocytes, 27 per cent.; eosinophiles, 3 per cent. Anemia; no nucleated red cells, some macrocytes and poikilocytes. Fever throughout the course of the disease, death in ten weeks. At autopsy a tumor of the right adrenal the size of a child's head; diagnosis, "malignant hypernephroma." Four metastases in the cranium, one very large, with complete erosion of the bone; metastasis in the axilla.

CASE VII. Richards (Case XXX of Richards' series). Male, aged six months. At the age of two months a lump appeared at the posterior fontanelle, and reached the size of a small orange; a similar tumor destroyed the right eye. Tumors also in the arm and leg. The autopsy showed three tumors of the calvarium, projecting both inward and outward, and covered with a thin shell of bone; other metastases in the fifth and sixth ribs, bronchial glands, liver, subcutaneous and muscular tissues of the arm and leg. Primary tumors 4 x 3 inches in both adrenals; histologically small round-cell sarcoma.

CASE VIII. Hutchison (I). Boy, aged eight years and nine months. Ecchymosis of left eye, headache and vomiting since a blow on the forehead five months before admission. Left cervical glands enlarged. A tumor in the left loin. The left eye later became protruded and the cornea destroyed. Tumor on the left tibia. Death in six months from onset. Autopsy: large tumor involving left kidney and left adrenal; calvarium infiltrated with growth. No secondary deposits elsewhere.

CASE IX. Hutchison (II). Boy, aged ten months. Swellings on the head first symptom; left eye protruded; hemorrhage into the orbit; provisional diagnosis scurvy. Died soon after admission. Reds, 3,125,000; whites, 12,000; no abnormal white cells. Autopsy: small round-cell sarcoma of the medulla of the left adrenal; calvarium and cervical glands infiltrated. No secondary deposits elsewhere.

CASE X. Hutchison (III). Boy, aged two and one-half years. Lumps noticed on the head five months before admission. Tumors of the forehead and temporal fossæ, ecchymosis and protrusion of the right eye-ball. The liver enlarged. Died six weeks after admission. Reds, 1,572,000; hemoglobin, 45 per cent.; whites, 14,500; polynuclears, 31 per cent. Autopsy: the right adrenal contained a tumor the size of a walnut. Secondary nodules in the liver and cervical glands; extensive growths in the calvarium and base of the skull. Microscopically, round- and oval-cell sarcoma.

CASE XI. Hutchison (IV). Girl, aged four years. Pains in the limbs and head for six months; great weakness. Tumor in the left hypochondrium. After admission optic neuritis, lumps on the forehead, and left-sided exophthalmos. Died three and one-half months after admission. Reds, 3,942,000; hemoglobin, 70 per cent.; whites, 10,500; polynuclears, 51 per cent. Autopsy: large nodular growth of the left adrenal, deposits in the lymph nodes all over the body, in the bones of the skull, and on the inner aspects of all the ribs but the first. The growth consisted of round and oval cells; the diagnosis was sarcoma or papilloma.

CASE XII. Hutchison (VI). Boy, aged three years. Ill two weeks, but pale for a considerable time. Hemorrhage from the gums. Growth in the left temporal fossa, slight exophthalmos. Optic neuritis, blindness. No tumor felt in the abdomen. Urine normal. Died nine weeks after the onset. Reds, 1,400,000; hemoglobin, 35 per cent.; whites, 8000; polynuclears, 65 per cent. Autopsy: sarcoma of the medulla of the left adrenal; infiltration of the calvarium and thoracic spine. Microscopically, round and oval-cell sarcoma.

CASE XIII. Hutchison (X). Boy, aged three years. Blackening of the left eye four weeks before admission; no history of injury. Double exophthalmos; both upper lids blackish; hemorrhage into the left conjunctiva. Ovoid elastic tumor on the right parietal bone and a rounded prominence above the right ear. Profound anemia. Spleen palpable. Urine normal. The abdomen became tender, but no tumor was felt. Died four weeks after admission. Autopsy: large tumor of left adrenal; the entire surface of the skull covered by huge masses of newgrowth, containing spicules of bone; invasion of both orbits. No deposits elsewhere. Microscopically, lymphosarcoma.

We have left out the case of Ogden and Mathews,[2] included by Hutchison in his table, on the ground that the adrenal origin, although probable, was not certain. The cranial metastases were, to be sure, quite characteristic, but the abdominal growth consisted of a large retroperitoneal mass involving the liver and upper pole of the kidney, no mention being made of the adrenal gland. Although this case, as well as those of Moreau[3] and Oshima,[4] may well have been of adrenal origin, the proof is lacking, and we believe it to be safer, in seeking to establish a new clinical syndrome, to keep to well established instances.

Reimann's case differs somewhat markedly from the others, both in the presence of melanotic pigment, and in the multiplicity and small size of the metastases. The diagnosis of carcinoma is open to question, such growths being more usually styled sarcomas, but the histological details are not complete enough to admit of exact classification. We have included it because the primary tumor was in the adrenal gland, and metastases to the skull were present, although small and not located in the orbit.

After this review of the literature, the question as to which of the tumors in our case was primary can be considered to better advantage. The identical histological appearances render it certain that all were of the same nature. The primary seat, however, cannot be decided from the gross or microscopic picture, for the cranial and abdominal tumors were both large, and the tumor cells showed no resemblance to adrenal tissue. It is well known, however, that a small tumor may give rise to enormous metastases, and in view of the inaccessible position of the adrenal, the failure to palpate the tumor during life is of no importance. Several lines of argument, nevertheless, lead us to regard the adrenal tumor as the primary one.

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[2] Brit. Jour. Childr. Dis., 1906, iii, 394.

[3] Bull. de la Soc. Anat. de Paris, 1852, 239.

[4] Wien. klin. Woch., January 24, 1907, 93.

In the first place, we have been unable to find instances in which a primary tumor of the cranium has caused metastases to the adrenal gland; and enlargement of the pre-auricular glands, so constantly met with in the group of cases under consideration, is exceptional in sarcoma of the orbit.[5]

Another point in favor of the adrenal origin is the well-known predilection of adrenal tumors to metastasize in the bones. This is especially true of the hypernephromas of adults, of which Scudder, in 1907, collected 17 instances with bone metastasis, to which we have been able to add 34 more, bringing the total up to 51. The great frequency of bone metastases in these tumors is even better brought out by a study of the cases followed to autopsy; thus, Albrecht found them present in 5 out of 11, and Böhler in 5 out of 10 autopsies. The relative frequency of bone metastases is, therefore, probably greater in the case of adrenal growths than in tumors of any other organ. The hypernephroma of adults, however, rarely causes exophthalmos, the metastases being situated in the skull fairly often, but almost never in the orbit (1 case of the 51 with bone metastases).

It would not do, however, to lay too much emphasis on the occurrence of bone metastases in hypernephroma, for this type of tumor shows a structure resembling that of the adrenal gland, and the group in question does not. It is very possible that the frequency of bone metastases might be because of the nature of the growth, not because of the location. For tumors of the lymphocytic series have a tendency to metastasize in tissues of a similar nature, that is, in the bone marrow and lymphoid structures. And the cells of the tumor in our own case resemble closely the myelocytes found in erythroblastic centres in bone marrow.

The final argument is derived from a critical study of the cases in the literature. No less than six, or almost one-half (Cases VI, VIII, IX, XI, XII, and XIII), show involvement only of the adrenal, the bones, and the lymph nodes. If it were assumed that the orbital tumor was the primary one, it would surely be very remarkable that it should in so many instances give metastases only to the suprarenal gland of all the viscera, whereas in the case of one form of adrenal tumor, the hypernephroma, solitary metastasis to the bony system is well established. Furthermore, in Richards' case both adrenals were the seat of tumors, which again would be exceptional on the assumption of metastasis, while the involvement of both glands in primary growths is not uncommon.

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[5] Cf. Lagrange, Tumeurs de l'œil et de l'orbite., Paris, 1904, vol. ii.

We, therefore, regard the adrenal tumor as primary in our case, which resembles closely those hitherto reported; Case XIII, in fact, appears identical with ours in every respect.

It remains to give a brief consideration of the other forms of adrenal tumor occurring in children. The second type, already referred to, is that of simultaneous sarcoma of the liver and adrenal. It has been well described by Pepper, and is met with as a congenital tumor in the first weeks of life; clinically there is enormous enlargement of the liver, without ascites, and, as a rule, without jaundice. The liver is sometimes involved alone, usually in company with the adrenal. Histologically there is in all instances a diffuse infiltration with small round-cell sarcoma.

The third type is extremely interesting with regard to the relation of the adrenal glands to the growth of the body, and to sexual development. The disease is chiefly seen in girls of one to eight years of age, and runs a comparatively slow course, usually of several years' duration. These children present a very remarkable appearance, the face and pubes being covered with an abundant growth of hair, and the external genitalia as fully developed as in the adult. They are obese and abnormally large for their age, a child of five years having the size and general appearance of a boy of sixteen (Linser's case). Pigmentation of the skin may occur, but the color is more like that of a brunette or gypsy than like the bronzing seen in Addison's disease. The intellect is dulled and the disposition sullen. Appetite, and sometimes thirst, are increased, and vomiting is likely to be an obstinate feature. The urine may contain albumin, due to the presence of blood, but sugar is absent. At autopsy a tumor of the adrenal gland is found, which is usually large, reaching up to 3 pounds (Fox's case).

Almost all of these tumors which have been examined histologically have shown a structure more or less resembling that of the normal adrenal gland, and, therefore, come into the group of the hypernephromas. This is important, as indicating the possibility of an increased adrenal secretion in these cases. And, indeed, in three instances (Otto,[6] Crecchio,[7] Marchand,[8]) premature development has been associated with simple hyperplasia of the adrenal glands.

Either precocious maturity, or giant growth, or both, have been found also in tumors of the pituitary and pineal glands, of the testes and ovaries; and retardation of growth has been associated with lack of development of the thyroid (cretinism), and of the adrenal glands. For this and other reasons all these glands may be assumed to have an intimate physiological connection with one another (Linser). Lack of space, however, forbids a further discussion of this interesting subject, fully dealt with in the articles of Linser, and Bullock and Sequeira, to which the reader is referred.

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[6] Path. Anat. Beobacht., 1816, 139. Quoted by Lancereaux. Dict. Encycl. d. Sciences Méd.

[7] Wien. med. Presse, 1866, Nr. 30, p. 763.

[8] Internat. Beiträge zur Wiss. Med., 1891, Band i. Festschrift f. Rudolf Virchow, p. 554.

Other tumors of the adrenal (Group IV) occur in children, but they show no distinctive clinical features, and, therefore, do not require a detailed consideration here. Sarcoma, carcinoma, glioma, and hypernephroma without precocious maturity, have all been observed. Rachmaninow[9] has reported several cases of mixed tumors of the adrenal, but the kidney was involved in all, so that they are more properly to be classified with the "congenital adenosarcoma of the kidney" described by Birch-Hirschfeld.

DIAGNOSIS. Tumors of the orbit in infants and young children should arouse the suspicion of metastases from an adrenal growth, and the abdomen should be carefully palpated; an abdominal tumor if present is almost sure to be of adrenal origin; the presence of enlarged pre-auricular glands renders primary sarcoma of the orbit unlikely. Chloroma presents almost identical growths, being associated with tumors of the orbit in two-thirds of the cases, with exophthalmos usually as the first symptom. It may be excluded by the absence of leukemic changes in the blood. Myeloma may cause bony growths about the skull, but is exceedingly rare in childhood; the presence of the Bence-Jones body in the urine would render the diagnosis of myeloma certain, while its absence is not conclusive.

An abdominal tumor associated with precocious maturity is practically certain to be of adrenal origin, if tumors of the ovaries or of a retained testis can be excluded. Other adrenal tumors in most cases cannot be distinguished from tumors of the adjacent tissues, especially of the kidney.

TREATMENT. The only hope lies in early radical removal, but unfortunately these tumors usually pass unnoticed until either their great size or the presence of metastases attracts attention, and then it is too late, as a rule, for a successful operation.

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CONGENITAL ABSENCE OF THE GALL-BLADDER.

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Mrs. M. was admitted to the Columbian Hospital July 19, 1907, with the following history: She was fifty-four years of age, had been sick from time to time during the past five years, and had a severe attack of typhoid fever ten years ago. At the beginning of her present illness she had symptoms of gastric ulcer. The gastric pain subsided, and later she had well-marked discoloration of her skin and other evidence of obstruction of her bile-ducts. Her appearance indicated poor nutrition, with marked anemia, and evident mischief about the gall-bladder or bile-ducts. On examination a mass could easily be outlined; this was thought to be the gall-bladder, and we were confident that several stones would be found. Operation was done on July 20, and the following conditions were observed: The gall-bladder was conspicuously absent, and the duodenum and pylorus were elevated and appeared to be attached along the notch which is usually the seat of the bladder. We soon located the stones, but were surprised to find them in what proved to be the hepatic and common ducts. It was necessary to divide the mesentery of the duodenum to reach the stones. Two stones were removed from the common and six from the hepatic duct. Both ducts were largely dilated. The stones were about the size of filberts. After removing the calculi we made a very careful search for the missing gall-bladder but without success. We discovered a papule very near the site of the cystic duct. Careful probing through the open hepatic duct failed to locate any vestige of the cystic duct. Although the patient had been sick for many years, there had been no well-marked attack of gallstone colic. The evidence of cholecystitis, with the resulting adhesions, was not present, and we were not confronted by the results of inflammation, as is so often the case; but, as we have already stated, the anatomical defects were distinctly peculiar. It was necessary to open the ducts widely in order to extract the stones. The patient had a slow recovery, due